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Functional basis for the glomerular alterations in uranyl nitrate acute renal failure

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Functional basis for the glomerular alterations in uranyl nitrate acute renal failure. We have examined the acute renal failure that occurs after uranyl nitrate administration in the rat and the specific effects of pretreatment of rats with angiotensin converting enzyme inhibitor (CEI), plasma volume expansion (PVE) after uranyl nitrate, and a combination of these treatments. We utilized a combination of micropuncture measurements of glomerular hemodynamics, cage studies, and histologic examination of renal tissue to evaluate the degree of acute renal failure in all groups studied. Uranyl nitrate (UN) (25 mg/kg body wt) administration caused a reduction in the nephron filtration rate (SNGFR) (39.4 ± 1.6 to 24.8 ± 2.9 nl · min^{-1} · g kidney wt^{-1}, $P < 0.02$) as a result of a major decrease in the glomerular ultrafiltration coefficient (LpA) from control values (≥ 0.085 ± 0.008 to 0.035 ± 0.007 nl · sec^{-1} · mm Hg^{-1} · g kidney wt^{-1}, $P < 0.01$). Treatments with CEI, PVE, and the combination of CEI and PVE in rats receiving UN restored LpA to normal values (> 0.061 ± 0.009, 0.091 ± 0.020, and 0.138 ± 0.020 nl · sec^{-1} · mm Hg^{-1} · g kidney wt^{-1}, respectively). Cage studies revealed that CEI treatment prevented oliguria and resulted in major volume losses and reduction in weight. However, rats died after a similar period after UN, but probably by different mechanisms. Analysis of renal ultrastructure revealed equivalent tubular damage in all experimental groups. Alterations in LpA after UN are functional in nature and are potentially preventable and reversible by a combination of treatments with CEI and PVE.

Base fonctionnelle des altérations glomérulaires au cours de l'insuffisance rénale aiguë par nitrate d'uranyl. Nous avons examiné l'insuffisance rénale aiguë qui survient après administration de nitrate d'uranyl chez le rat et les effets spécifiques du pré-traitement des rats par un inhibiteur de l'enzyme de conversion (CEI), par une expansion du volume plasmatique (PVE) après le nitrate d'uranyl, et par l'association de ces traitements. Nous avons utilisé une combinaison de mesures par microponction de l'hémodynamique glomérulaire, d'études en cage, et d'examen histologique des tissus rénaux afin d'évaluer le degré d'insuffisance rénale aiguë dans tous les groupes étudiés. L'administration de nitrate d'uranyl (UN) (25 mg/kg poids corp) a réduit le débit de filtration néphronique (SNGFR) (39,4 ± 1,6 à 24,8 ± 2,9 nl · min^{-1} · g rein poids^{-1}, $P < 0.02$), conséquence d'une diminution importante du coefficient d'ultrafiltration glomérulaire (LpA) des valeurs contrôles (≥ 0,085 ± 0,008 à 0,035 ± 0,007 nl · sec^{-1} · mm Hg^{-1} · g rein poids^{-1}, $P < 0.01$). Les traitements par CEI, PVE, ou l'association CEI et PVE chez les rats recevant UN a restauré LpA à des valeurs normales (> 0,061 ± 0,009, 0,091 ± 0,020, et 0,138 ± 0,020 nl · sec^{-1} · mm Hg^{-1} · g reins poids^{-1}, respectivement). Les études en cage ont révélé que le traitement par CEI empêchait l'oligurie et aboutissait à des pertes importantes de volume et à une réduction du poids. Cependant, les rats mourraient après une période identique après UN, mais probablement par des mécanismes différents. L'analyse de l'ultrastructure rénale a révélé des altérations tubulaires équivalentes dans tous les groupes expérimentaux. Les altérations de LpA après UN sont de nature fonctionnelle et sont potentiellement prévenues et réversibles par une association de traitement avec CEI et PVE.

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In 1975, micropuncture studies from our laboratory revealed that the reduction in kidney glomerular filtration rate that occurs within a few hours after the administration of either 15 or 25 mg/kg body wt uranyl nitrate (i.v.) was the result of two renal events: *1)* significant transepithelial backleak of solutes as large as inulin across damaged tubules beyond the mid-proximal tubule; and *2)* a major reduction in the glomerular ultrafiltration coefficient (LpA), the product of glomerular hydraulic conductance (Lp), and ultrafiltering surface area (A) [1]. These studies represented the first direct and quantitative demonstration of a reduction in LpA in an experimental model of acute renal failure. Separate but parallel studies during the past decade have also demonstrated that naturally occurring hormonal substances can lead to reductions in LpA [2]. In 1976, our laboratory examined the effects of intravenous angiotensin II and found that in addition to the well-documented increase in renal vascular resistances, angiotensin II produced a major reduction in the glomerular ultrafiltration coefficient by influencing either or both capillary hydraulic conductance and glomerular surface area [3]. Certain altered physiologic states have been associated with reductions in LpA, and there is reasonable evidence that angiotensin II may be involved in this process [2]. A specific morphologic and mechanical explanation for the action of angiotensin in affecting LpA has not been delineated. However, studies have demonstrated angiotensin II receptors within glomeruli [4], and glomerular mesangial cells in culture do respond to angiotensin II by contracting [5]. A variety of studies also suggest that angiotensin II effects upon LpA are readily reversible and not dependent upon permanent architectural alterations [6–8].

The basic hypotheses to be tested in the current study are: *1)* the decrease in LpA that occurs after uranyl nitrate administration is functional in origin, and *2)* the LpA effects in this model

of acute renal failure may be either preventable or reversible with treatments such as converting enzyme inhibition and plasma volume expansion, maneuvers which reduce the intrarenal generation of angiotensin II [9, 10].

Methods

Studies were performed with male Munich-Wistar rats (190 to 290 g), bred and maintained in a colony housed at the Animal Research Facility, Veterans Administration Medical Center, San Diego, California, USA. Animals were fed standard rodent chow (#5001, Ralston Purina Company, St. Louis, Missouri, USA) until 16 hrs prior to micropuncture, but were permitted free access to water. Rats were anesthetized with Inactin (100 mg/kg body wt, i.p.) Surgical preparation was as described previously [3, 11, 12]. All maintenance infusions were administered via a jugular vein catheter (P.E. 50). In all groups, a separate infusion of ^{14}C inulin ($\cong$ 40 μCi/hr) dissolved in isotonic sodium chloride and sodium bicarbonate (0.5% to 0.7% body wt/hr) was begun 1 hr prior to the measurement period.

Hydropenic groups

Four groups of hydropenic rats were studied; all received a total infusion rate of 0.5 to 0.7% body wt prior to and throughout micropuncture measurements. Hydropenic control rats (N = 15) received maintenance infusion and no pretreatment or other infusions. Measurements of glomerular capillary (P_G) and Bowman's space (P_{BS}), as well as peritubular capillary hydrostatic pressures (HP_E), were performed with a servo-nulling device using 1 to 2 μm tip pipets. Methods of pressure measurement and the mechanics of the pressure monitoring device have been described in previous publications from this laboratory [3, 11, 13]. Samples of tubular fluid were collected from early segments of proximal tubules for measurement of single nephron glomerular filtration rate (SNGFR). At least three samples of efferent peritubular capillary blood from "star" vessels were obtained for measurement of protein concentration. Mean arterial blood pressure (MAP), whole kidney glomerular filtration rate (GFR), and hematocrit (HCT) were measured throughout the period.

In a second group, hydropenic rats (N = 7) were pretreated with uranyl nitrate (UN) 90 min prior to micropuncture surgery. The UN was administered via a subcutaneous (SQ) injection in the back using a dose of 25 mg UN/kg body wt. All other measurements followed the protocol for hydropenic control rats.

The third hydropenic micropuncture group used (N = 6) was constituted by rats pretreated 2 to 4 days with CEI (converting enzyme inhibitor) drinking water (33 mg captopril/100 ml H_2O, SQ14,225, Squibb & Sons, Princeton, New Jersey, USA) ad libitum. These rats were deprived of food for 16 hrs prior to surgery. Rats were infused with 1 mg CEI/ml in isotonic sodium chloride and sodium bicarbonate solution (1 mg captopril/kg body wt/hr) initiated within 20 to 30 min after anesthesia. The inulin infusion rate and concentration were adjusted to guarantee that the rat received the same total volume as supplied to rats in the other two hydropenic groups (0.5% to 0.7% body wt/hr). All other aspects of the protocol were identical to the hydropenic control group.

Another group of six hydropenic rats were submitted to CEI treatment using the same protocol, but received no UN. The single effect of CEI upon SNGFR and the determinants thereof were assessed in this group using identical micropuncture techniques.

Three groups of seven hydropenic rats were maintained in metabolic cages with free access to standard rodent chow and water. One group served as a normal control. The next two groups received 25 mg/kg body wt UN subcutaneously to reproduce the dose and mode of administration used in the micropuncture studies. One of these UN groups received oral CEI in drinking water from 2 days prior to UN injection until 7 days after or time of death. Daily weights and urine outputs were monitored in each group and recorded.

Plasma volume expansion groups

In three groups, a plasma volume expansion (PVE) protocol was utilized using 2.5% body wt littermate plasma and 1.25% body wt isotonic sodium chloride and sodium bicarbonate solution infused over 1 hr [3, 13]. The plasma infusion was followed by additional saline-bicarbonate solution at a rate 20 μl/min in excess of total urine flow rate to maintain the volume status. Standard inulin infusion of $\cong$ 40 μCi/hr (0.5 to 0.7% body wt/hr) was begun at the initiation of PVE and continued throughout the measurement period in the PVE control group (N = 10). All measurements were identical to those obtained in the hydropenic control group. A second group (N = 6) followed the same protocol as in PVE control group, but was pretreated with UN 3 hrs prior to PVE. Ninety min prior to surgical preparation, each rat was injected with 25 mg UN/kg body wt subcutaneously. All micropuncture measurements were obtained in this UN-PVE group as in the hydropenic control group.

The third PVE group utilized rats pretreated 2 to 4 days with CEI water (N = 6). Rats were injected subcutaneously with UN (25 mg/kg body wt) 90 min prior to surgery with continued free access to CEI water. An infusion of CEI (1 mg captopril/ml saline-bicarb/kg body wt/hr) was begun 20 to 30 min after anesthesia. The plasma expansion protocol commenced with the concurrent administration of CEI and inulin. The inulin volume and concentration were adjusted to deliver the same radioisotope level per hr while compensating for the CEI infusion volume. All other aspects of the protocol for this UN-PVE-CEI group were identical to the hydropenic control group.

Micropuncture measurements

At least four to six measurements of nephron filtration rate (SNGFR) were obtained from each rat. Samples were collected from early to midportions of surface proximal tubules to avoid underestimation of SNGFR, since much of tubular damage and a presumed region of tubular "backleak" of inulin has been noted in later portions of the proximal tubule [1, 14, 15]. After insertion of a small mineral oil block (3 to 4 tubule diameters) via a 8 to 11 μm tip glass pipet, the collections were spontaneous throughout the time period. Care was taken to prevent alterations in tubular diameter during the collection.

In all groups, total urine volume was collected in preweighed containers under oil. From the radioactivity in both urine and plasma samples, the total kidney inulin clearance (C_{In}) was determined for right and left (micropuncture) kidneys.

Earlier studies demonstrated that little or no inulin "backleak" occurred within the accessible proximal tubule after UN administration since SNGFR obtained in early proximal segments did not differ from those obtained from late proximal tubular collections. To validate the quantitative accuracy of SNGFR collections after UN, further studies were conducted. Hydropenic rats were utilized that received UN 90 min prior to micropuncture surgery. ^3H inulin was added to isotonic NaCl-$NaHCO_3$ solutions to achieve count rates of ~ 14 cpm/nl of solution. Utilizing a Hampel microperfusion pump, this solution was added to the normal flow in early proximal tubular segments and timed collections obtained from the last accessible proximal segment. Control perfusions were conducted into H_2O containing vials to determine 100% recovery rates of inulin. Control perfusions were interspersed with tubule perfusions and data expressed as inulin recovery as a percentage of control perfusion inulin values.

Analytic methods

Nephron filtration rate (SNGFR) was calculated from the total counts of [^{14}C] inulin in tubular fluid sample divided by the plasma counts per nanoliter and the time of the collection. Specifics of the microprotein method have been described in detail in prior publications [11, 12]. Plasma and urine electrolytes were determined on a flame photometer (Instrumentation Laboratory, Inc., Lexington, Massachusetts, USA).

Calculations

The nephron plasma flow (SNPF) is calculated as follows:

$$SNPF = SNGFR/(1 - C_A/C_E)$$

where C_A is the systemic protein concentration, C_E is the efferent peritubular capillary protein concentration as determined by microprotein methods and $(1 - C_A/C_E)$ = the nephron filtration fraction (SNFF = SNGFR/SNPF). The nephron blood flow (SNBF) is computed as described [3]. Afferent arteriolar resistance (AR) is defined as

$$AR = (MAP - P_G)/SNBF$$

where MAP = mean arterial blood pressure and P_G = glomerular capillary hydrostatic pressure, measured directly in mm Hg. Efferent arteriolar resistance (ER) is defined by the relationship

$$ER = (P_G - HP_E)/(SNBF - SNGFR)$$

where HP_E is large efferent peritubular capillary hydrostatic pressure.

The determinants of SNGFR are defined as follows:

$$SNGFR = LpA \cdot \overline{EFP}$$

where mean effective filtration pressure = $\overline{EFP}$. EFP along the glomerular capillary length (x*) (where x* = x/l and l = capillary length) is described as follows:

$$EFP_{x^*} = (\Delta P - \pi)_{x^*}$$

where π = oncotic pressure (mm Hg), which is related to C (gm/100 ml) as follows:

$$\pi = 1.76C + 0.28C^2 \text{ [1, 12, 16]}$$

a simplification of the empirical relationship described by Landis and Pappenheimer [17].

The $\overline{EFP}$ is defined as follows:

$$\overline{EFP} = {}_0\int^1 (\Delta P - \pi)dx^*$$

The EFP_{x^*} curve and LpA are determined by an iterative method as described previously from this laboratory [11, 12].

Morphologic studies

In a separate group of rats, tissues were taken for morphologic analysis. The surgical protocol, infusions, and time course were identical to the micropuncture groups described previously, but without ^{14}C inulin administration. At the conclusion of each experiment, a 2.5% glutaraldehyde in 0.075 M sodium cacodylate-HCl buffered fixative solution was infused via a P.E. 160 catheter inserted in the aorta just distal to the left renal artery. The aorta was clamped above the renal arteries before fixation and the kidney was then briefly flushed with 3 to 5 ml of isotonic sodium chloride-sodium bicarbonate solution to clear the kidneys of blood cells. Both renal veins were clipped while flushing with the isotonic solution, then the fixative was infused via the same catheter through a three-way teflon valve. The infusion pressure was monitored throughout the fixation (80 mm Hg) with a perfusion of 8 to 10 ml/min for 4 to 5 min. After 30 to 40 ml of fixative was infused, the kidneys were removed, bisected, and immediately placed in small vials of fixative. The vials were coded randomly in a single-blind protocol and sent to one of the authors' laboratories for morphologic analysis (A.P.E.). Tissues remained in the fixative for 2 to 4 days.

After in situ tissue fixation, portions of the entire cortex of the kidney were removed and further fixed in the original fixative for a minimum of an additional 48 hrs. Subsequently, the tissue was prepared for and quantitated by light microscopy and transmission electron microscopy as described previously [13, 18]. All renal samples were assigned numbers and read without knowledge of the experimental regimens.

Light microscopic examination was performed on tissue that was routinely dehydrated and embedded in JB-4 media (Polysciences, Inc., Warrington, Pennsylvania, USA). The tissue was sectioned at 4 μm with a JB-4 microtome (DuPont-Sorvall, Inc., Newton, Connecticut, USA) and stained with toulidine blue. The sections were viewed on a Leitz laborlux 12 microscope with a 40 × objective and 10 × eyepiece (Midland, Ontario, Canada).

Morphological changes in the nephrons of the different experimental groups were determined by a semiquantitative histologic analysis [19, 20]. For each of the proximal, distal, and cortical collecting tubular segments, we examined 50 individual tubular cross sections per animal and scored the severity and distribution of the lesions by the following scale: 0 = absence of the lesion; 1 = lesion represented in less than 10% of the tubules and with minimal injury; 2 = lesion represented in up to 25% of the tubules and with moderate injury; 3 = lesion represented in

Table 1. Glomerular hemodynamics in control rats, rats receiving uranyl nitrate (25 mg/kg body wt), and rats receiving uranyl nitrate and treatments with converting enzyme inhibitor (CEI) and plasma volume expansion

Group	MAP	P_G	P_{BS}	ΔP	HP_E	C_{In} $ml \cdot min^{-1} \cdot g$ kidney wt^{-1}
	mm Hg					
Hydropenia (N = 15)	115[a] ± 2	47.5[a] ± 0.7	13.8[a] ± 0.5	33.7[a] ± 0.4	19.3[a] ± 0.5	1.12[a] ± 0.04
Hydropenia, uranyl nitrate pretreatment (N = 7)	107[b] ± 3	51.1 ± 1.9	10.8 ± 1.8	40.3[b] ± 1.6	16.6 ± 3.7	0.56[b] ± 0.14
Hydropenia, uranyl nitrate and CEI pretreatment (N = 6)	83[bc] ± 2	45.8 ± 2.6	10.8 ± 1.6	35.0 ± 1.8	10.4[b] ± 1.9	0.38[b] ± 0.07
Plasma volume expansion (N = 10)	125[bc] ± 2	58.5 ± 0.9	20.9[b] ± 0.6	37.6[b] ± 0.6	22.7[b] ± 0.9	1.51[bc] ± 0.05
Plasma volume expansion, uranyl nitrate pretreatment (N = 6)	115 ± 6	53.4 ± 2.5	15.6 ± 1.4	37.8[b] ± 1.5	22.1[b] ± 1.0	0.82[b] ± 0.05
Plasma volume expansion, uranyl nitrate and CEI pretreatment (N = 6)	105 ± 5	58.3 ± 3.4	23.1[b] ± 2.0	35.2 ± 1.8	25.8[b] ± 2.0	1.05[c] ± 0.10

[a] Values are expressed as the mean of the average values derived for each animal ± SEM, N refers to number of animals studied.
[b] Significantly different from the control value ($P < 0.02$).
[c] Significantly different from the uranyl nitrate value ($P < 0.05$).
[d] At filtration pressure equilibrium ($\Delta P \approx \pi_E$), therefore, a minimum estimate, ≥.

25 to 50% of tubules with moderate injury; 4 = lesion on 50 to 90% of the tubules with moderate injury; and 5 = lesion represented in over 50% of the tubules and with severe injury. Minimal injury was defined as a loss of the brush border and amorphous debris in tubular lumen while moderate injury included cell swelling and vacuolization. Severe injury was noted by a loss of epithelial cells from tubular wall. Five animals were examined from each experimental group.

For transmission electron microscopy, small pieces (1 mm cubes) of cortical tissue were postfixed in 1% OsO_4 in 0.075 M cacodylate-HCl buffer for 1½ hrs, rinsed in the cacodylate buffer, and dehydrated through a series of graded ethanols. Subsequently, the tissue was passed through two changes of propylene oxide, embedded in Epon 812, and cured at 60°C for 24 to 48 hrs. Sections were cut at 60 to 90 nm on an LKB ultramicrotome III (LKB Instruments, Inc., Rockville, Maryland, USA) with a diamond knife and stained with uranyl acetate and lead citrate. The tissue was examined and photographed with a Phillips EM 400 Electron Microscope (Phillips Electronic Instruments, Inc., Mahwah, New Jersey, USA).

Statistical analysis

Statistical analysis of physiologic data utilized analysis of variance and unpaired analysis where appropriate as described previously [11, 13, 21].

Results

The administration of uranyl nitrate did not alter the appearance of the kidney surface in either hydropenic rats or those rats which had undergone plasma volume expansion after uranyl nitrate. As noted in a prior publication [1], uranyl nitrate administration was associated with a modest initial increase in urine volume, however, at the time of micropuncture (3 to 4 hrs post injection), urine volumes did not differ significantly from the untreated hydropenic control rats (1.7 ± 0.1 μl/min in control, 2.3 ± 0.7 μl/min with UN in hydropenia, and 2.0 ± 0.4 μl/min with UN + CEI in hydropenia). Urine flow was increased in plasma volume expansion + UN (29.4 ± 5.2 μl/min, $P < 0.05$), and CEI + plasma volume expansion after UN (34.8 ± 8.4 μl/min, $P < 0.05$) when compared to control plasma volume expansion (7.2 ± 0.6 μl/min), possibly as a result of UN induced tubular damage.

Studies in the hydropenic rat

Uranyl nitrate administration to hydropenic rats resulted in a significant decrease in SNGFR to 24.8 ± 2.9 nl · min^{-1} · g kidney wt^{-1} compared to 39.4 ± 1.6 nl · min^{-1} · g kidney wt^{-1} in normal hydropenic controls ($P < 0.01$) (Table 1). This decrease in SNGFR was accompanied by an even greater decrease in C_{In} from 1.12 ± 0.04 to 0.56 ± 0.14 ml · min^{-1} · g kidney wt^{-1} ($P < 0.01$), the greater reduction in C_{In} undoubtedly the result of transepithelial backleak of inulin beyond the mid-proximal tubule, as demonstrated previously in this experimental model of acute renal failure [1]. The reduction in SNGFR was, in major part, the consequence of a decrease in LpA from a minimum estimate of 0.085 ± 0.008 nl · sec^{-1} · mm Hg^{-1} · g kidney wt^{-1} in control hydropenic rats at filtration pressure equilibrium to 0.035 ± 0.007 nl · sec^{-1} · mm Hg^{-1} · g kidney wt^{-1} after uranyl nitrate administration ($P < 0.01$) (Table 1). Filtration pressure equilibrium was not attained in hydropenic rats that received uranyl nitrate. The nephron plasma flow was also somewhat decreased when compared to control hydropenic levels. AR was, however, unchanged by UN administration, but ER numerically increased from 11.8 ± 1.2 to 16.8 ± 2.3 dyne · sec · $cm^{-5} \times 10^9$ ($0.1 > P > 0.05$). MAP was significantly but modestly decreased after UN (115 ± 2 vs. 107 ± 3 mm Hg, $P < 0.05$), which contributed to the decrease in SNPF (Table 1). The glomerular capillary hydrostatic pressure gradient (ΔP) actually increased after uranyl nitrate (33.7 ± 0.4 vs. 40.3 ± 1.6 mm Hg, $P < 0.01$), which counteracted a portion of the negative effects of decreased LpA upon the SNGFR after UN. In summary, UN decreased SNGFR primarily through a major reduction in LpA. This influence of decreased LpA upon SNGFR was therefore partially attenuated by the concomitant increase in ΔP.

Table 1. *Continued*

SNGFR	SNPF	SNBF	SNFF	π_A	π_E	AR	ER	EFP_A	EFP_E	$\overline{EFP}$	LpA
nl·min^{-1}·g kidney wt^{-1}				*mm Hg*		*× 10^9 dyne · sec · cm^{-5}*		*mm Hg*			*nl · sec^{-1} g · kidney wt^{-1}· mm Hg^{-1}*
39.4[a]	117[a]	271[a]	0.35[a]	16.9[a]	32.9[a]	22.2[a]	11.8[a]	16.6[a]	0.8[a]	8.0[a]	0.085[ad]
± 1.6	± 8	± 19	± 0.01	± 0.4	± 1.0	± 1.8	± 1.2	± 0.5	± 1.0	± 0.6	± 0.008
24.8[b]	88[b]	202[b]	0.28[b]	19.2	31.9	22.9	16.8	21.2	8.5	15.3	0.035[b]
± 2.9	± 10	± 23	± 0.01	± 0.8	± 1.8	± 2.3	± 2.3	± 2.3	± 3.1	± 2.9	± 0.007
24.3[b]	74[b]	168[b]	0.34	20.0	38.1	18.3	20.6	15.0	−3.2	7.1	0.061[cd]
± 1.9	± 8	± 19	± 0.03	± 1.0	± 2.6	± 1.8	± 1.9	± 2.0	± 3.9	± 2.5	± 0.009
63.7[bc]	264[bc]	461[bc]	0.25[b]	22.2	34.7	12.4[bc]	8.0[c]	15.4	2.9	8.6	0.128[bc]
± 3.4	± 26	± 43	± 0.02	± 0.6	± 1.2	± 1.4	± 1.2	± 0.8	± 0.8	± 0.6	± 0.010
37.3[c]	174[bc]	297[c]	0.23[b]	22.8	34.8	17.4	11.4[c]	15.0	3.0	8.4	0.091[cd]
± 1.8	± 16	± 33	± 0.03	± 0.9	± 5.1	± 2.4	± 1.7	± 1.5	± 2.4	± 1.9	± 0.020
46.0[bc]	212[bc]	396[bc]	0.23[bc]	23.2	34.8	10.1[bc]	7.7[bc]	12.0	0.4	6.0	0.138[bcd]
± 2.4	± 25	± 44	± 0.02	± 1.0	± 1.9	± 1.8	± 0.8	± 1.1	± 2.2	± 1.3	± 0.020

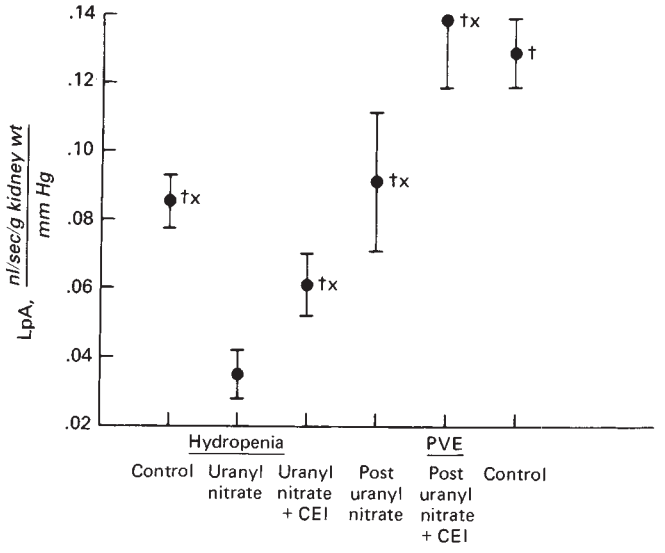

Fig. 1. *A comparison of values for the glomerular ultrafiltration coefficient in each of the control and experimental groups.* Groups in which filtration pressure equilibrium was attained ($\Delta P \approx \pi_E$) are designated by the symbol (X), and the values for LpA are minimum possible values. In the remaining groups, filtration pressure equilibrium was not attained and the values for LpA are exact values. The symbol (†) designates those treatment groups in which LpA was significantly increased above values in rats receiving uranyl nitrate alone. Uranyl nitrate, therefore, decreases LpA and treatments with CEI and PVE restores LpA to at least control values.

Table 2 demonstrates data on the effects of CEI alone in both hydropenic rats and rats which have undergone plasma volume expansion (PVE). In hydropenic rats, CEI causes a reduction in MAP, yet SNGFR is reasonably well maintained. CEI does not specifically increase LpA. In fact, there is a tendency in hydropenic rats with intact renal innervation for LpA to decrease slightly after CEI administration [7, 22]. The mechanism of this apparent small decrease in LpA in innervated hydropenic rats remains to be elucidated. It is clear that CEI administration does not produce a non-specific increase in LpA in the normal rat.

Pretreatment with CEI exerted several major effects upon glomerular function in rats receiving UN. The combination of CEI pretreatment and UN administration resulted in a further and major decrease in MAP to 83 ± 2 mm Hg ($P < 0.01$), values also significantly lower than UN rats. C_{In} (0.38 ± 0.07 ml/min, $P < 0.01$) and SNGFR were also decreased below control values in UN rats receiving CEI. The persistent reduction in SNGFR was due to a continued low value for SNPF (74 ± 8 nl · min^{-1} · g kidney wt^{-1}, $P < 0.01$) and a lesser value for ΔP than observed in UN rats (35.0 ± 1.8 mm Hg). The major continued reduction in C_{In} was undoubtedly largely the result of persistent "backleak" of inulin across damaged tubules beyond the proximal tubule [1]. These rats, in contrast to rats receiving UN alone, attained filtration pressure equilibrium for at least two reasons: the continued lower SNPF due to the reduction in MAP, and an increase in LpA (minimum estimate) to 0.061 ± 0.009 nl · sec^{-1} · mm Hg^{-1} · g kidney wt^{-1} ($P < 0.05$) compared to UN rats, NS compared to control hydropenic values (Fig. 1). CEI pretreatment prevented the UN reduction in LpA but did not restore SNGFR to normal because of the reduced values for SNPF, secondary to further reductions of MAP, and the lesser value for ΔP when compared to the elevated values in UN rats. Continued tubular "backleak" also contributed to the persistent reduction in C_{In} as evidenced by the greater percentage reduction in GFR than SNGFR.

Twenty-five mg UN/kg body wt was given to two groups of awake rats ($N = 7$): *1)* rats receiving UN alone; and *2)* rats injected with UN on continuous CEI drinking water ($N = 7$); and a control group that received neither UN nor CEI ($N = 7$). Four of the seven UN rats became oliguric after 2 days. None of the rats treated with CEI became oliguric, in fact, urine volume was normal to high for the first 4 to 5 days. In spite of the maintenance of urine output in the CEI treated rats, mortality was 100% within 7 days, whereas only three of seven UN rats died within this period. This finding may be explained

Table 2. Effect of converting enzyme inhibitor (CEI) administration on the determinants of nephron filtration rate in normal hydropenic and plasma volume expanded (PVE) rats

	MAP	SNGFR	SNPF	ΔP	π_A	π_E	LpA
	mm Hg	*nl · min⁻¹ · g kidney wt⁻¹*		*mm Hg*			*nl · sec⁻¹ · g kidney wt⁻¹ · mm Hg⁻¹*
Hydropenic control rats (N = 15)	115 ± 2	39.4 ± 1.6	117 ± 8	33.7 ± 0.4	16.9 ± 0.4	32.9 ± 1.0	0.08[a] ± 0.01
Hydropenic rats pretreated with CEI for 48 hr (N = 6)	88 ± 5	37.6 ± 3.5	115 ± 21	34.2 ± 1.5	13.5 ± 0.5	27.1 ± 0.5	0.05 ± 0.004
Hydropenic rats[b] pretreated with CEI for 14 days (N = 6)	72 ± 5	29.8 ± 5.8	141 ± 30	30.6 ± 2.6	17.2 ± 1.4	24.8 ± 1.5	0.07 ± 0.02
Hydropenic rats[c] with acute CEI infusion (N = 6)	93 ± 1	34.5 ± 1.2	107 ± 4	34.6 ± 0.7	16.7 ± 0.9	30.6 ± 1.0	0.05 ± 0.03
PVE control rats (N = 10)	125 ± 2	63.7 ± 3.4	264 ± 26	37.6 ± 0.6	22.2 ± 0.6	34.7 ± 1.2	0.13 ± 0.01
PVE after CEI pretreatment (N = 6)	111 ± 3	55.8 ± 1.8	198 ± 16	39.7 ± 0.9	20.9 ± 0.5	35.7 ± 1.1	0.10 ± 0.02

[a] Filtration pressure equilibrium.
[b] From [36].
[c] From [7].

by differences in volume status, as reflected by changes in body wt. In rats receiving UN alone, body wt decreased by −4.1 ± 1.9% by 7 days or time of death, compared to a −0.6 ± 2.0% change in untreated control rats. However, rats that received UN and treatment with CEI incurred a decrease in body wt of −17.6 ± 1.7%, values significantly greater than either control or UN rats ($P < 0.01$). These results demonstrate that chronic CEI treatment does not prevent death from UN-induced acute renal failure, in spite of the early beneficial effects of CEI treatment. However, the mechanisms producing death may differ in that the combination of UN administration and CEI treatment leads to greater degrees of volume depletion, possibly by maintaining a higher initial GFR in the setting of continued tubular damage.

Studies in rats submitted to plasma volume expansion

Values for SNGFR, C_{In}, and all of the pertinent pressures, flows, and resistances in control plasma volume expanded rats, rats undergoing plasma volume expansion (PVE) within 3 to 4 hours after UN administration, and rats pretreated with CEI, which received UN and were later submitted to PVE (UN-PVE+CEI), also appear in Table 1.

In rats that received UN and were submitted to PVE, SNGFR increased to values not different from hydropenic untreated controls (37.3 ± 1.8 vs. 39.4 ± 1.6 nl · min^{-1} · g kidney wt^{-1}), but significantly higher than rats receiving UN alone (24.8 ± 2.9 nl · min^{-1} · g kidney wt^{-1}, $P < 0.01$). However, C_{In} remained lower than untreated hydropenic control rats, (0.82 ± 0.05 vs. 1.12 ± 0.04 ml · min^{-1} · g kidney wt^{-1}), in rats undergoing PVE after UN administration, probably as a result of continued "backleak" of inulin across damaged epithelia beyond the proximal tubule in rats receiving UN. Post-UN PVE restored SNGFR to the normal untreated values by at least two mechanisms: *1)* the SNPF increased to 174 ± 16 nl · min^{-1} · g kidney wt^{-1}, values significantly higher than both untreated controls ($P < 0.02$) and rats receiving UN ($P < 0.01$); and *2)* a major increase in LpA to 0.091 ± 0.020 nl · sec^{-1} · mm Hg^{-1} · g kidney wt^{-1}, values higher than in rats receiving UN (0.035 ± 0.007 nl · sec^{-1} · mm Hg^{-1}, $P < 0.01$) and equal to values in untreated control rats (0.085 ± 0.008 nl · sec^{-1} · mm Hg^{-1} · g kidney wt^{-1}, NS) (Fig. 1). ΔP was not significantly different from UN treated rats. Therefore, PVE within 3 to 4 hours after UN also restored LpA to values not different from normal control, an effect also observed with CEI pretreatment alone.

Data depicted in Table 2 demonstrates that CEI does not further increase the LpA in rats submitted to PVE. Also, other determinants of SNGFR are not significantly influenced by CEI in normal rats after PVE. The combination of CEI pretreatment and PVE after UN administration resulted in an even higher value for SNGFR (46.0 ± 2.4 nl · min^{-1} · g kidney wt^{-1}, $P < 0.01$ compared to untreated control rats), but these values remained lower than untreated PVE control rats (63.7 ± 3.4 nl · min^{-1} · g kidney wt^{-1}, $P < 0.01$). C_{In} was 1.05 ± 0.10 ml · min^{-1} · g kidney wt^{-1} in this group, a value similar to the hydropenic, untreated rats, but significantly lower than PVE control rats that did not receive UN (1.51 ± 0.05 ml · min^{-1} · g kidney wt^{-1}, $P < 0.01$). LpA was again increased to values much higher than in rats receiving UN only (0.138 ± 0.020 nl · sec^{-1} · mm Hg^{-1} · kidney wt^{-1}), but values not significantly different from rats undergoing PVE after UN (both "normal" values) (Table 1). The reason that SNGFR in CEI pretreated rats receiving UN and undergoing PVE remained lower than untreated PVE control rats was a lesser value for SNPF. This decrease in SNPF was the result of a significantly lower value for MAP rather than a result of any differences in either afferent or efferent arteriolar resistance.

Both plasma volume expansion after UN administration and PVE plus CEI pretreatment resulted in an increase in LpA to normal values in rats that had received UN. SNGFR and SNPF were also increased to values equal to or greater than untreated hydropenic control rats (Table 1). C_{In} tended to remain lower in rats that received UN, undoubtedly as a result of continued transepithelial "backleak" of inulin.

Inulin recovery was utilized as an index of transepithelial "backleak" after UN in this study. In 19 tubules in the hydropenic condition after UN, the mean recovery of inulin

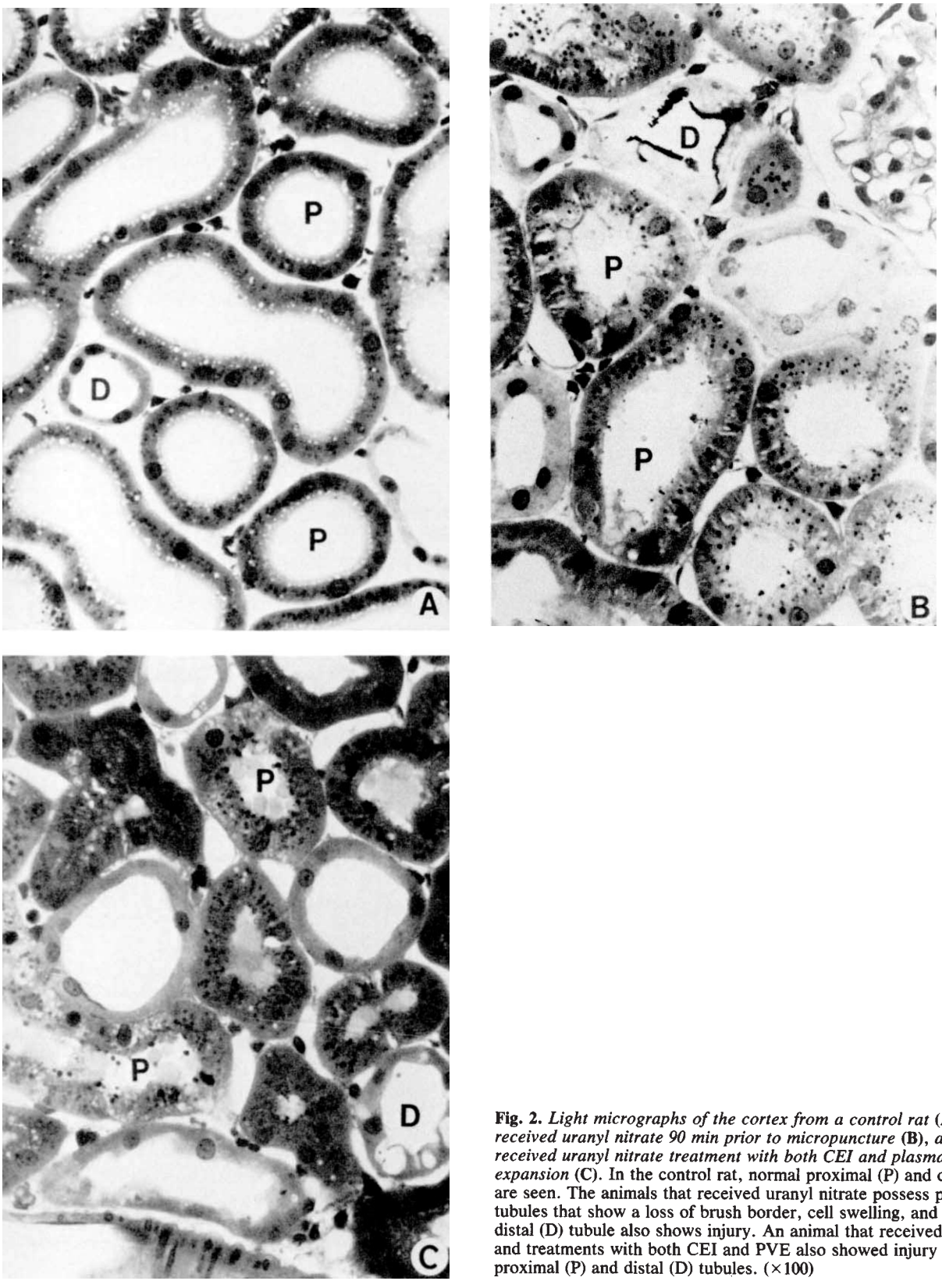

Fig. 2. *Light micrographs of the cortex from a control rat* (**A**), *animal that received uranyl nitrate 90 min prior to micropuncture* (**B**), *and rats that received uranyl nitrate treatment with both CEI and plasma volume expansion* (**C**). In the control rat, normal proximal (P) and distal (D) tubules are seen. The animals that received uranyl nitrate possess proximal (P) tubules that show a loss of brush border, cell swelling, and vacuolization. A distal (D) tubule also shows injury. An animal that received uranyl nitrate and treatments with both CEI and PVE also showed injury to some proximal (P) and distal (D) tubules. (×100)

added to early proximal tubule segments was 96.0 ± 2.7%, when compared to control perfusions. This value of 96% was not different from 100% (NS), demonstrating no significant "backleak" along the accessible proximal tubule.

Renal morphology

The morphology of the visceral epithelial cells of the renal corpuscle appeared similar for all experimental conditions and identical to the control state, as observed by transmission electron microscopy.

Obvious cell injury in proximal, distal, and cortical collecting tubules was observed in many nephrons, regardless of the experimental condition (Figs. 2 and 3). The severity and distribution of the injury was determined by a semiquantitative histologic analysis to be similar for all protocols when compared to controls (Table 3).

The injured cells were characterized by a loss of microvilli, cell swelling, numerous vacuoles of various sizes, enlarged lysosomes, and occasionally swollen mitochondria (Figs. 2 and 3). The cell injury was not localized to a particular segment of the proximal tubules in that all segments (S_1, S_2, and S_3) were affected. Cast material was noted in the proximal distal collecting tubules (Fig. 3).

The LpA was definitely decreased only in the group of rats that received UN and no other treatments. The word, definitely, was used to signify that since filtration pressure equilibrium was not attained in rats receiving UN alone, in spite of the lower values for nephron plasma flow, an exact value for LpA could be defined (Table 1). In several of the other experimental groups, filtration pressure equilibrium was attained and only a minimum estimate of LpA could be defined. However, even these values were significantly higher than the value in rats receiving only UN (Fig. 1).

Table 3. Semiquantitative histologic analysis of severity and distribution of cell injury in proximal, distal, and collecting tubules of control and experimental groups

Treatment	Proximal tubules	Distal tubules	Collecting tubules
Control ($N = 5$)	0[a]	0	0
Uranyl nitrate (UN) ($N = 5$)	2.5[b]	3.0[b]	2.5[b]
UN and CEI ($N = 5$)	2.5[b]	2.7[b]	2.5[b]
UN and PVE ($N = 5$)	2.2[b]	3.0[b]	2.5[b]
UN and PVE + CEI ($N = 5$)	2.5[b]	2.5[b]	2.5[b]

N, number of animals studied.
[a] Values expressed as mean pathological score.
[b] Statistical significance was determined by two-way analysis of variance. All experimental groups were statistically similar when compared to the controls, $P < 0.05$.

Discussion

A reduction in the glomerular ultrafiltration coefficient (LpA) has been demonstrated to be a major factor contributing to the decrease in glomerular filtration rate, which has been observed in various experimental models of acute renal failure [1, 23, 24]. The nephrotoxic form of acute renal failure that results from the administration of uranyl nitrate represents one of the earliest direct demonstrations of a reduction in LpA [1, 25]. Since uranyl nitrate produces significant renal cellular injury [1, 14, 15], it might be assumed that such alterations in LpA are irreversible. However, the results of the present study demonstrate this conclusion is not justified. Pretreatment of rats with converting enzyme inhibitor and the combination of converting enzyme inhibitor and plasma volume expansion results in normalization of LpA and, in the latter case, of nephron filtration rate.

The initial studies from this laboratory on the mechanism of reductions in GFR after uranyl nitrate determined that both tubular and glomerular events contributed to this process [1]. Inulin "backleak" was demonstrated as a consequence of uranyl nitrate-induced late proximal tubular damage. The reduction in LpA could also have resulted from glomerular accumulation of uranium, however, it has been impossible to demonstrate uranium in glomerular structures [1, 15]. Morphologic analysis in this study revealed equivalent degrees of tubular damage in all groups that received UN, and physiologic data suggested that the greater reduction in whole kidney C_{In} observed in rats receiving UN was likely the result of persistent tubular inulin "backleak" beyond the accessible proximal tubule, an element apparently unaffected by CEI and PVE [1].

A specific mechanism whereby tubular damage is linked to the reductions in both nephron filtration rate and LpA has not been defined in this model (tubular obstruction is minimal in this form of acute renal failure). The physiologic results of this study do suggest that the events at the glomerulus, the reduction in LpA, can be functionally separated from the tubular damage resulting from UN by treatments with either or both CEI and PVE.

CEI pretreatment in rats receiving UN was sufficient to restore LpA to values indistinguishable from normal at filtration pressure equilibrium, however, examination of the data in Table 1 reveals that neither SNGFR nor whole kidney C_{In} was restored to normal values in UN rats by CEI pretreatment alone. The SNGFR remained lower than control because of a reduction in nephron plasma flow (SNPF), which resulted from a decrease in mean arterial pressure in rats receiving both CEI and UN and an inadequate autoregulatory adjustment of afferent arteriolar resistance. The lower MAP in this group of 83 mm Hg was undoubtedly multifactorial, resulting from the urinary volume losses after UN, documented in this study and our previous study [1], and the combined effects of CEI and UN on peripheral vascular resistance. The continued subnormal value for whole kidney C_{In} was due to the above effects on SNGFR and the documented transepithelial backleak of solutes as large as inulin in areas of damaged epithelium beyond the proximal tubule. We have demonstrated previously that if inulin was microinjected into proximal tubules of rats receiving UN, major losses of inulin occurred prior to the final urine [1]. However, since nephron filtration rates collected in early and late proximal tubular segments were not different, no significant "backleak" of inulin was demonstrated across the accessible surface proximal tubules. In the current analysis, when inulin-containing solutions were perfused into early proximal tubule segments of rats that received UN, recovery of inulin from late proximal tubule segments was nearly 100%, in spite of the apparent tubular damage. From the results of the current study, it is clear that CEI pretreatment and PVE did not prevent either tubular damage or back diffusion of inulin out of damaged tubules, an important contribution to the final C_{In}. It is clear, however, that CEI did prevent the UN-induced reduction in LpA. CEI does not increase LpA in the normal rat to supranormal values (Table 2).

In the other experimental groups receiving UN, PVE after

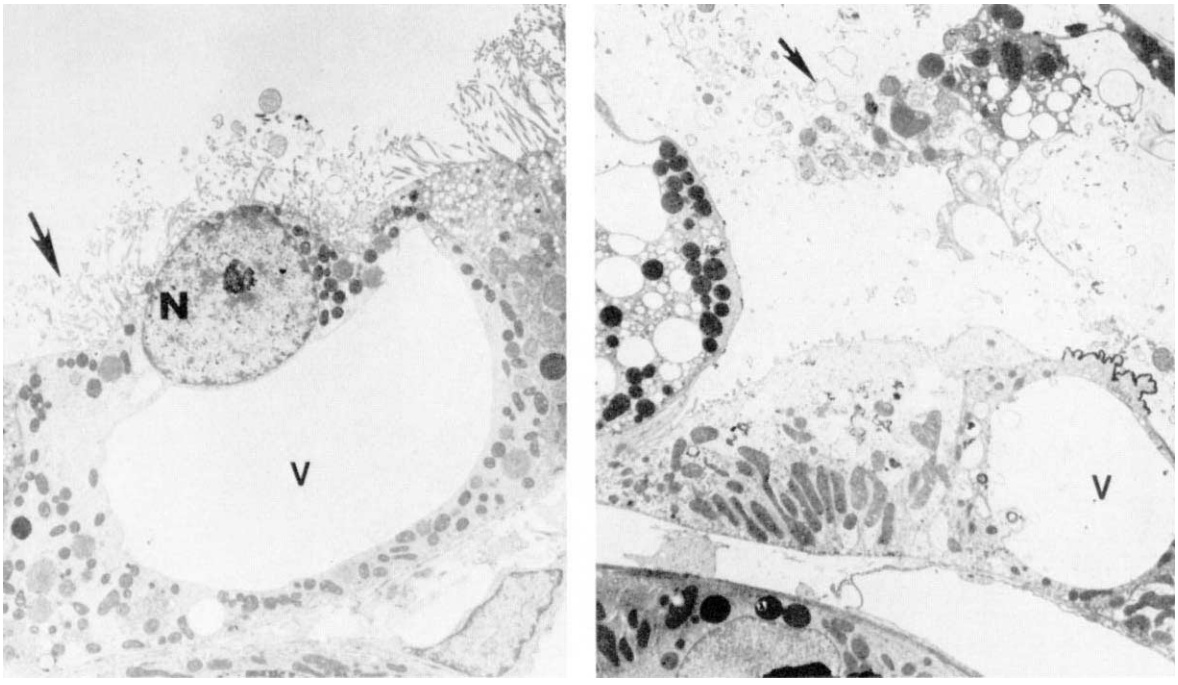

Fig. 3. *The appearance of proximal convoluted* (left) *and distal tubules* (right) *by transmission electron microscopy after 90 min of uranyl nitrate administration.* The proximal tubule on the left demonstrates a loss of apical microvilli (*arrow*) and an enormous vacuole (V), which has displaced the nucleus (N) and mitochondria. The distal tubular cells on the right exhibit numerous large vacuoles (V), suggesting cell injury. Cellular debris (*arrows*) is also found within the tubular lumen, denoting cellular necrosis. Cellular injury of proximal and distal tubular cells was approximately equal in all groups of rats that received uranyl nitrate, regardless of further treatment with CEI, PVE, and the combination of treatments. (×3,000).

UN administration and the combination of PVE and CEI pretreatment, LpA was also restored to values that should be considered "normal" for the rat. SNGFR was restored in these groups to at least the normal hydropenic control values (Table 1). This restoration of SNGFR to normal was in part the consequence of a normalization of LpA, but also the result of a maintenance of a more normal value for MAP and nephron plasma flow. The fact that values for SNGFR remained lower than values for SNGFR in rats submitted to PVE only, may be the result of acute volume losses incurred by rats receiving UN, a finding documented in this study and in our original study on this issue [1]. Based upon the ratio of SNGFR to total kidney GFR, one might conclude that PVE also reduced the degree of inulin "backleak". Inulin "backleak" is not only a function of the degree of tubular damage, but also a function of the transtubular inulin concentration gradient, which would undoubtedly be lower in PVE than hydropenia, a factor which exerted an apparently more beneficial effect on GFR in PVE treated rats.

The physiologic results of this study imply a role for angiotensin II in the reduction in LpA that occurs after UN administration. Both converting enzyme inhibition and plasma volume expansion are likely to decrease intrarenal angiotensin II activity [9, 10]. Angiotensin II has been demonstrated capable of producing a reduction in LpA [3, 6, 8, 26]. Certain studies have suggested that mesangial cell contraction in response to angiotensin II may underlie this decrease in LpA [5]. Alternatively, the physiologic effects of both CEI treatment and PVE are multifactorial and may involve other processes that may effect the apparent functional link between tubular damage and glomerular dysfunction, that is, influences on tubuloglomerular feedback mechanisms. Baylis and co-workers have demonstrated that gentamicin administration in rats resulted in a decrease in nephron filtration rate that was largely the result of reductions in the glomerular ultrafiltration coefficient, K_f or LpA [24]. In later studies from this same laboratory, Schor et al demonstrated that chronic pretreatment with an oral converting enzyme inhibitor prevented the gentamicin-induced reductions in LpA and nephron filtration rate [27]. The results of these studies and the current investigation would suggest that reductions in intrarenal angiotensin II activity can lead to prevention of the functional reduction in the glomerular ultrafiltration coefficient in at least two separate and distinct forms of nephrotoxic acute renal failure.

The issue of the role of angiotensin II in experimental acute renal failure has undergone considerable revision since first proposed as a basis for "vasomotor nephropathy" [28]. The study on uranyl nitrate acute renal failure from this laboratory was one of several studies that demonstrated that increased renal vascular resistance and major reductions in nephron blood flow were not necessary for the major reduction in glomerular filtration rate in acute renal failure [1]. The results of this study do suggest that prevention of renal angiotensin II generation can provide major beneficial effects in a model of acute renal failure without exerting an effect on nephron blood flow. To the extent that reduced intrarenal AII mediates the beneficial effects of CEI and PVE, the effects of AII must be localized to the glomerular capillary and LpA. A reasonable explanation for

the apparently selective glomerular capillary effects of angiotensin II is that uranium may prevent the renal vascular response at the arteriolar resistance vessels. This speculation is supported by the apparent lack of renal autoregulatory vasodilation in response to reductions in blood pressure in rats receiving UN (Table 1). Although morphologic changes within the glomerulus have been reported after UN [29], there is no evidence that AII influences glomerular endothelial cells.

A reasonable explanation for the functional link between tubular damage and alterations in glomerular function involves the tubuloglomerular feedback mechanism. Tubular damage after UN probably decreases transport of NaCl and water in the proximal nephron. Increases in the rate of delivery of tubular fluid and NaCl to the distal nephron results in reduction in nephron filtration rate and may alter AII generation [30]. Studies from several laboratories have shown that these feedback-induced changes in SNGFR are due to changes in vascular resistances, resulting in alterations in nephron plasma flow and glomerular capillary pressure [31, 32] and, in certain circumstances, alterations in LpA or K_f [33]. To an extent, suppression of angiotensin II activity does inhibit the full or normal expression of tubuloglomerular feedback activity [32, 34, 35]. As noted previously, CEI and PVE suppress both angiotensin II and tubuloglomerular feedback activity, such that the tubuloglomerular feedback mechanism remains a potential explanation linking tubular damage to the functional alteration in nephron filtration rate and LpA. However, such treatments may also alter basal activity of other systems, such as renal adrenergic activity and prostaglandin generation.

Cage studies on the effects of CEI in rats receiving UN were of interest. As observed in our prior study, most rats receiving UN developed oliguria within 2 to 3 days after administration of UN and several died within 5 days. CEI treatment largely prevented the development of oliguria, probably by maintaining SNGFR in the face of major tubular damage. In fact, rats receiving UN and CEI became significantly volume depleted as indexed by an acute reduction in body wt of ~ 18%. CEI did not prevent death after UN but, in all probability, these animals died, in part, as a result of volume depletion.

The current study demonstrates that the reduction in glomerular ultrafiltration coefficient (LpA) after uranyl nitrate is functional in nature in that changes can be largely prevented by prior administration of angiotensin converting enzyme inhibitor and normalized by plasma volume expansion and a combination of these two treatments. These functional glomerular changes occurred in spite of equivalent degrees of tubular damage observed in all experimental groups receiving uranyl nitrate. Results are compatible with the hypothesis that glomerular alterations may be due either to the intrarenal generation of angiotensin II or the activation of the tubuloglomerular feedback mechanism.

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